REMARKS

This Amendment is filed in response to the non-final Office Action dated May 19, 2009, and is respectfully submitted to be fully responsive to the rejections raised therein. Accordingly, favorable reconsideration on the merits and allowance are respectfully requested.

In the present Amendment, claims 14 and 23 have been amended to be within the scope of the working examples in the present application. Specifically, claims 14 and 23 have been amended to delete the phraseology "an N oxide thereof, a solvate thereof or a prodrug thereof." Claim 23 has been further amended to limit the scope of the claim to exemplary compounds of Formula (I-3-4) which are provided in the present specification.

Specifically, the scope of claim 23 has been amended to the compound of Formula (I-3-4), wherein R^2, R^3, R^6, R^7, R^{103} individually represents a hydrogen atom; X^1 and Z^1 represent a single bond; Y^1 represents-C(=O)-, -C(=O)NR^{103}-, -SO_2-, -C(=O)O- or SO_2NR^{103}; and B represents C_{1-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl which may be substituted with 1 to 4 substituent(s) optionally selected from hydroxyl, mercapto, amino, carboxyl, nitro, cyano, mono- or di-C_{1-6} alkylamino, C_{1-6} alkoxy, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylthio, a halogen atom, acyl, or benzene which may be substituted with 1 to 4 substituent(s) optionally selected from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, a carbocyclic ring, a heterocyclic ring, hydroxyl, C_{1-8} alkoxy, amino, $NR^{104}R^{105}$, carboxyl, C_{1-6} alkoxycarbonyl, nitro, cyano, a halogen atom, oxo, acyl, formyl and tri(C_{1-6} alkyl)silyl.

No new matter has been added. Support for the amendments can be found, e.g., in original claims 14 and 23, the exemplary compounds listed in the specification, and page 4, lines 11-15 (wherein R^6 and R^7 each represent a hydrogen atom).

Entry of the Amendment is respectfully submitted to be proper. Upon entry of the Amendment, claims 1-21 and 23-25 will be pending in the application.

I. Information Disclosure Statement

As an initial matter the Office Action indicates that Applicants' Information Disclosure Statement (IDS) filed December 22, 2005 fails to comply with 37 C.F.R. §1.98(a)(2). According to the Examiner, the foreign patent documents that have been lined-through have been placed in the application file without consideration.

Applicants respectfully submit that the IDS filed December 22, 2005, the submission of the references were based on an International Search Report. However, to advance prosecution, Applicants concurrently submit herewith an IDS listing the corresponding English publication/patent of the "lined-through" references. Consideration of these references are respectfully requested.

Furthermore, Applicants respectfully submit that the Office Action summary erroneously indicates that two Information Disclosure Statements were filed; one on March 2, 2007 and the other on December 22, 2005. It appears that the IDS filed March 2, 2007 was inadvertently scanned into in the present application. That is, application number 10/561,973, entitled "Conveyor System with Pivotable Hooks", which is listed on the IDS dated March 2, 2007 is not the present application.

II. Election/Restriction

In the instant Office Action, for examination purposes the Examiner has created groups V(a) and V(b) based on the formula recited in claim 23. The Examiner indicated that the elected species of claim 25 falls within Group V(a), and therefore Group V(a) was examined on the merits.

Applicants respectfully submit that in Formula (I-3-2) wherein R^{6-1} and R^{7-1}, which correlate to R^6 and R^7 in Formula (I-3-4), do not combine to form a ring, necessarily represent substituents. *See*, Specification, page 21, lines 8-11, for example. Therefore, claim 23 has been amended to recite that R^6 and R^7 in Formula (I-3-4) each represent hydrogen atoms. Applicants submit that claim 23 as amended is their species election. Support for the amendment can be found in the Specification on page 4, lines 11-15.

III. Response to Rejection - 35 U.S.C. § 112

Claims 14-18, 23, and 24, are rejected under 35 U.S.C. §112, first paragraph as assertedly lacking enablement with respect to various substituents for X^1, Y^1, Z^1, B, R^6, R^7, R^1, and the solvates or prodrugs of the same.

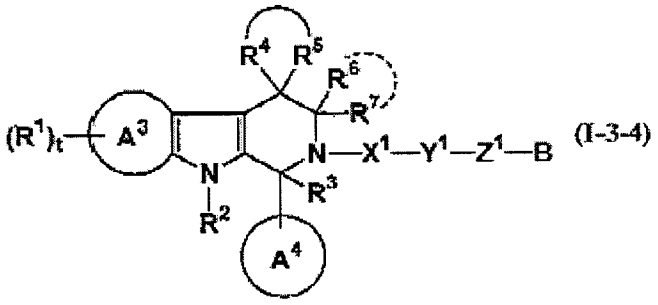
Applicants respectfully traverse and request that the rejection be withdrawn in view of the amendment to the claim and the following remarks.

To satisfy enablement, the specification must enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention without undue experimentation. Thus, the relevant test of enablement is not whether any

experimentation is necessary, but whether, if experimentation is necessary, it is *undue*. Factor to determine whether experimentation is undue include: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

How to Make

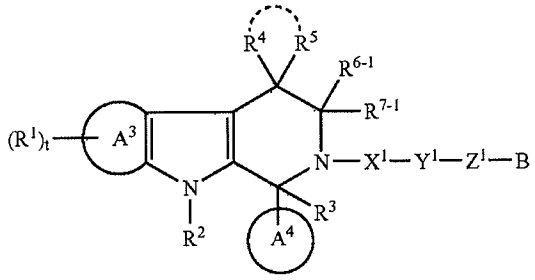
The presently claimed invention is directed to compounds and pharmaceutical compositions for diseases caused by stress. Relevantly, claim 23 recites a compound represented by formula (I-3-4), shown below:



(I-3-4)

In view of the election of 2-acetyl-1-(3-fluorophenyl)-1,2,3,9-tetrahydrospiro[β-carboline-4,1'-cyclopropane] as a species election, the Examiner has broaden the search for examination purposes to include groups V(a), which is based on Formula (I-3-2) below.

(I-3-2)



The relevant question is whether the specification is enabling with respect to compounds having the formula (I-3-2) wherein X^1 and Z^1 represent, e.g., C1-3 alkylene, C2-3 alkenylene, or C2-3 alkynylene; Y^1 represents -C(=S)-, -C(=O)NR^{103}-, -SO_2-, -C(=O)O-, or SO_2NR^{103}- , B is a hydrocarbon or a cyclic group (carbocyclic or heterocyclic ring); R^6 and R^7 represent C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, a carbocyclic ring, a heterocyclic ring, hydroxyl, C1-8 alkoxy, mercapto, C1-8 alkylthio, amino, $NR^{104}R^{105}$, carboxyl, C1-6 alkoxycarbonyl, nitro, cyano, a halogen atom, oxo, acyl, formyl or tri(C1-6alkyl)silyl.

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without *undue* experimentation.[2] The presently claimed compound and compositions thereof are subgenus of the compound of formula (I).[3] The present disclosure teaches that the compounds of formula (I) can be prepared by processes described in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition" "Richard C. Larock, John Wiley & Sons Inc., 1999".

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[2] MPEP § 2164.02.

[3] *See* Specification (U.S. 2006/0154944), p. 2, [0014].

Specifically, the specification discloses that compounds of formula (I) wherein X is a single bond, Z is present, and Y may represent -C(=O)-, -C(=O)NR^{103}-, -SO_2-, -C(=O)O-, or SO_2NR^{103}-; i.e., the compound of Formula (IA), are prepared by reacting the compound of formula (II) with the compound of formula (III) in an organic solvent under the presence of a base at temperatures from -20° C to reflux, for example.[4]

Formula (IB) are compounds of the present invention wherein X is a single bond, Z is present and Y represents -C(=O)NR^{103}- or -C(=S)NR^{103}-. The specification discloses how to make the compounds of formula (IB) by reacting the compound of formula (IV) with the compound of formula (V) in an organic solvent under the presence of a base at a temperature of 0° C to reflux, for example.[5]

In view of the above, Applicants respectfully submit that the present specification discloses processes of making the presently claimed compounds and compositions wherein Z is a single bond; Y represents -C(=O)-, -C(=O)NR^{103}-, -SO_2-, -C(=O)O-, SO_2NR^{103}-, or -C(=S)NR^{103}-; and Z and B are the groups as recited in the claim.

Next, the specification also describes the process of making the compounds and compositions of the presently claimed invention wherein X may represent an optionally substituted C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene; Y is -C(=O)-, -C(=O)NR^{103}-, -SO_2-, -C(=O)O-, SO_2NR^{103}-; and Z and B are the groups as recited in the claim. Specifically, these compounds are represented by formula (ID) and are made by reacting the compound of formula

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[4] *See*, Specification at p. 20, paragraphs [0294] to [0296].

[5] *See*, Specification at p. 21, paragraphs [0311] to [0318]; see also, [0319] to [0323].

(II) with the compound of formula (VIII) in an organic solvent under the presence of a base and under the presence or in the absence of a catalyst at a temperature of 0° C to reflux, for example.[6]

Furthermore, the specification also teaches that the starting materials (i.e., II, III, IV, V, etc.) may be prepared by known processes described in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition" "Richard C. Larock, John Wiley & Sons Inc., 1999".[7]

Moreover, the specification contains over seventy-five (75) working examples of processes of making and the characterization of the presently claimed compounds. The working examples include N-phenylacetamide derivatives; i.e., wherein X^1 is C_1 alkyl and Y^1 is -C(O)NR^{103}-; and benzyl carboxylates wherein X^1 is a bond, Y^1 is -COO- and Z^1 is C_1 alkyl; Example 7 and Example 8, respectively. *See also*, Examples 17 and 26. Particularly, Example 17(8) and 17(9) disclose the characterizations of 2-acetyl-1-(3-fluorophenyl)-1,2,3,9-tetrahydrospiro [β-carboline-4,1'-cyclobutane] and 2-acetyl-1-(3-fluorophenyl)-1,2,3,9-tetrahydrospiro [β-carboline-4,1'-cyclopentane], respectively, which were made by the same procedure as described in Example 17 using the corresponding amine derivatives.[8]

Applicants submit that the present specification clearly describes compounds of formula (IA) wherein A is a ring A1, which is a heterocyclic ring including at least one nitrogen atom, or wherein A1 represents a tricyclic heterocyclic ring; X is a single bond, Y is –C(=O)-, -

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[6] *See*, Specification at p. 23, paragraphs [0324] to [0326].

[7] See, Specification at p. 24, paragraph [0338].

[8] *See* Specification, p. 47, paragraphs [0755], [0758]; and p. 48, paragraphs [0772] - [0776].

$C(=O)NR^{103}$-, SO_2-, -C(=O)O-, SO_2NR^{103}- can be obtained from reaction of the compound of formula (II) and the compound of formula (III), as a general production method for various substituents. Thus, for the above-mentioned reasons the specification provides the methods of making the compounds according to claim 23.

How to Use

The present specification discloses how to use the compounds and compositions to treat diseases caused by stress and that the compounds, in combination with other pharmaceutical preparations, can be administered to the entire human body or topically, and orally or parenterally. The dosage of the compounds to be administered depends on age, body weight, symptom, therapeutic effect, etc.

The specification also teaches that the presently claimed compounds have an affinity for mitochondrial benzodiazepine receptors (MBR), which is useful for prevention and/or treatment for diseases caused by stress and that MBR antagonist can inhibit steroid production in the brain. The specification discloses that the affinity of the present claimed compounds to the MBR was determined using rat brain membrane. Specifically, the results of the receptor binding experiment show that the presently claimed compounds had a high affinity to MBR. Furthermore, the anti-stress effects on Winstar rats were evaluated. This is disclosed in the present specification as Biological Example 2. The results of the evaluation show that the compound of the presently claimed invention had anti-stress effects on the laboratory experimental mice.

Accordingly, Applicants submit that one skilled in the art would know how to make and use the compound of Formula (I-3-4) for the entire scope of claim 23 based on the

description in the specification as set forth above, including the citation of "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition" "Richard C. Larock, John Wiley & Sons Inc., 1999", which the disclosures of said reference has been incorporated in the present specification.

Furthermore, the specification further describes pharmacological experiments comprising the compounds wherein R^4 and R^5 form a ring (i.e., cyclopropyl), namely, the compound in Example 17 shows high affinity to MBR and shows anti-stress effects. Additionally, the fact that a compound having high affinity to MBR shows anti-stress effect is described in US 2005/0009812 A. Additionally, animal models used in the evaluation of anti-stress effects reflects effectiveness for irritable bowel syndrome (IBS) as described in publications such as *Brain Res.*, 641, 21-28 (1994) and *Jpn. J. Pharmcol.* 77, 211-217 (1998). Thus, a person skilled in the art would know that the present compounds, having high affinity to MBR are useful for stress related disease such as IBS and the like.

A copy of *Brain Res.* and *Jpn. J. Pharmcol.* are submitted along with other references in an Information Disclosure Statement (IDS).[2]

Nevertheless, without acquiescing to the merits of the rejection and to advance prosecution, Applicants have amended the present claims to delete the non-elected subject matter and recite compounds of Formula (I-3-4) based on exemplary compounds provided in the specification.

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[2] Applicants note that an IDS is not required as these references are submitted solely in order to support Applicants' arguments in response to the Office Action. Nevertheless, as an IDS is submitted to provide copies of the references listed in the December 22, 2005 IDS, copies of the above two references are included in the IDS.

Accordingly, withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

IV. Response to Provisional Non-statutory Double Patenting

Claims 23-25 and 14-18 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-29 of co-pending Application No. 11/722623 (the '623 application). The rejection is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants respectfully request that the rejection be held in abeyance until allowable subject matter is indicated in one of the applications.

Furthermore, Applicants submit that the application is now believed to be in condition for allowance. Thus, Applicants request withdrawal of the provisional non-statutory double patenting rejection because the '623 application has a later effective filing date (December 21, 2005) than the instant application (June 22, 2004).

V. Claim 25

In the Office Action Summary, claim 25 is indicated as being objected. Claim 25 is rejected under non-statutory double patenting rejection, according to the detailed Office Action, and thus the status indication of claim 25 in the Summary appears to be incorrect. Clarification is respectfully requested.

VI. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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